Engineering in vitro models that reproduce tumor microenvironment and mimic functions and responses of tissues that is more physiologically relevant represents a potential bridge to cover the gap between animal models and clinical studies. In this talk, we describe nanostructured thin films as templates to develop biomimetic tissue-engineered technologies for cancer research. Our model systems enables us to examine the impact of dynamics changes in the physical environment of tumor microenvironment (TME) in conjunction to tumor-stromal (fibroblasts, mesenchymal stem cells (MSCs), immune cells) cell interactions to potentially mimic stable disease and/or its eventual progression to advanced stages. Tumors actively modulate their microenvironment by recruiting MSCs, lymphocytes and macrophages; vascular endothelial cells; and tumor-associated stromal cells such as fibroblasts. Tumor progression results in dynamic changes in the cell-cell interaction and tumor biology. Currently, the impact of key tumor-stromal cell interactions is unknown due to the lack of models or approaches that can address this key question.

In this study, we report a robust, inexpensive, protein free method that utilizes polyelectrolyte multilayers (PEMs) and capillary force lithography (CFL) to generate patterned co-culture models of breast cancer cells and stromal cells. PEMs have been shown to be excellent candidates for biomaterial applications. In our study, we used synthetic polymers, namely poly(diallyldimethylammoniumchloride) (PDAC) and sulfonated poly(styrene) (SPS) as the polycation and polyanion, respectively, to build the multilayers. We as well others have previously shown that PEM surfaces utilizing PDAC and SPS also provide an ability to control the arrangement of multiple cell types with subcellular resolution. This technique allows the formation of cell patterns with different shapes and sizes of tunable directional properties, recreating cell-cell interactions in a highly controlled manner. In this study, we capitalized upon the differential cell attachment and spreading of breast cancer cells on different PEM surfaces to engineer patterned co-cultures of breast cancer cells and stromal cells. To demonstrate the translational validity of our platform, we employed two developmentally distinct human breast cell lines for co-culture development: 1) BT474 (HER2+ invasive breast cancer cells to model invasive ductal carcinoma (IDC)), and 2) 21MT-1 (stable patient-derived metastatic breast cancer cells isolated from the metastatic pleural effusion to model invasive mammary carcinoma (IMC)). We also used two different types of stromal cells, mammary epithelial cells (MCF10A) and mesenchymal stem cells (MSCs) to demonstrate the versatility of our platform. Since MCF10A are non-tumorigenic cells and MSCs have a significant role in metastasis, our platform provides an opportunity to study cell-cell interactions in a heterogeneous TME, an inimitable property of cancer progression. We further illustrated that our in vitro breast tumor model is capable of staging the breast tumor dynamics and emulating clinical relevant molecular pathways at different stages of tumor points. For this purpose, we utilized the co-culture system developed in this study and demonstrated that our platform simulated key clinical markers prominently used for tumor diagnosis, including tumor (HER-2) and proliferation (Ki67) markers. Also our platform mirrored the clinical conditions when probed for miRNA-21 and miRNA-34 expression. The development of such in vitro models that recapitulates the in vivo like signaling in tumor would be desirable to increase the drive towards precision medicine to identify key biomarkers for early diagnosis and novel therapeutic interventions.